UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/936,702	09/13/2001	Edward A. Berger	4239-60771	9274

36218 7590 11/25/2003

KLARQUIST SPARKMAN, LLP
121 S.W. SALMON STREET, SUITE #1600
ONE WORLD TRADE CENTER
PORTLAND, OR 97204-2988

EXAMINER	
ZEMAN, ROBERT A	

ART UNIT	PAPER NUMBER
1645	8

DATE MAILED: 11/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/936,702	BERGER ET AL.	
	Examiner	Art Unit	
	Robert A. Zeman	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,11-12,14-19,23-40,48,49 and 52-55* is/are pending in the application.

4a) Of the above claim(s) *2-6,35,36 and 38-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,11,12,14-19,23-34, 37, 48,49 and 52-55* is/are rejected.

7)☒ Claim(s) *14 and 16* is/are objected to.

8)☒ Claim(s) *1-6,11,12,14-19,23-40,48,49 and 52-55* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4 and 6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment and response filed on 8-22-2003 is acknowledged. Claims 1, 11, 14, 19, 23-24, 33-34 and 48-49 have been amended. Claims 7-10, 13, 20-22, 41-47 and 50-51 have been canceled.

Election/Restrictions

Applicant's election with traverse of Group II in Paper No. 7 is acknowledged. The traversal is on the ground(s) that:

- The claims of Group III are required to be classified in the same Group as the claims of Group II since the subject matter of both groups are linked to form a single general inventive concept.
- The amended claims are drawn to a specific category of bispecific fusion proteins. Said fusion proteins are capable of binding to two sites on gp120 wherein the first binding domain is derived from a CD4 molecule and the second binding domain comprises a binding portion of a variable region of an antibody heavy or light chain.
- The claims of Group VI are drawn to a specific example of the fusion proteins of Groups II and III.
- Groups VII, IX, X and XII are drawn to nucleic acids encoding the aforementioned fusion proteins and hence is considered to have unity with claims reciting the encoded proteins.
- Amended claims 19, 23 and 24 should be rejoined as they recite specific types of fusion proteins encompassed by claim 1.

Applicant's arguments have been fully considered and deemed to be persuasive with regard to the rejoinder of Groups II and III and claims 19,23 and 24. However, Applicant's arguments with regard to the groups containing claims drawn to nucleic acids and transgenic cells are deemed to be non-persuasive.

This is not found persuasive because while the proteins and nucleic acids share a technical feature, said technical feature is not deemed special since the bispecific molecules encoded by the claimed nucleic acids were known in the art.

The requirement is still deemed proper and is therefore made FINAL.

It should be noted that if claims reciting a given fusion protein are found to be free of the art of record, the corresponding nucleic acid claims will be rejoined.

Therefore, claims 2-6, 35-36, and 38-40 are withdrawn from consideration as being drawn to non-elected inventions. Claims 1, 11-12, 14-19, 23-34, 37, 48-49 and 52-55 are currently under examination.

Claim Objections

Claim 14 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 14 recites the limitation "wherein the second binding domain comprises a binding domain of an antibody". Said recitation does not further limit the parent claim (claim 1) which recites the limitation "and the second binding domain comprises a binding portion of the of a variable region of an antibody heavy or light chain".

Claim 16 is objected to because of the following informalities: Claim 16 recites nomenclature that is inconsistent with the specification and other claims (claim 33). Claim 16 recites the Markush group of SCFv17b. SCFv48d and SCFvCG10. The specification and claim 33 refer to SCFv17b, for example, as SCFv(17b). Appropriate correction is required.

Specification

The use of the trademark QIAexpress (see page 19) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see page 14). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16, 18, 33-34 and 37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that neutralizing monoclonal antibodies 17b, 48d and CG10 (claim 18) and the single-chain Fvs SCFv17b. SCFv48d and SCFvCG10 (claims 16, 33-34 and 37) are required in order to practice the claimed invention. The deposit of said biological materials is considered by the Examiner to be necessary for the enablement of the current invention (see 37 CRF 1.808(a)).

If the deposit is made under terms of the Budapest Treaty, then an affidavit or declaration by Applicants or person(s) associated with the patent owner (assignee) who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty *and* that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit, or declaration by Applicants or person(s) associated with the patent owner (assignee) who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the following criteria have been met:

1) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

2) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent; and

3) the deposits will be maintained for a term of at least thirty (30) years from the date of the deposit or for the enforceable life of the patent or for a period of at least five (5) years after the most recent request for the furnishing of a sample of the deposited material, whichever is longest; and

4) a viability statement in accordance with the provisions of 37 CFR 1.807; and

5) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition, the identifying information set forth in 37 CRF 1.809(d) should be added to the specification. See 37 CFR 1.803 – 1.809 for additional explanation of these requirements.

Claims 1, 11-12, 14-19, 23-32, 48-49and 52-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for neutralizing bispecific fusion proteins capable of binding to an inducing site on gp120 (CD4 binding site) thereby exposing an induced epitope of gp120 (co-receptor binding site) and a second binding domain capable of forming a neutralizing complex with the induced epitope wherein the first binding domain is sCD4 (soluble CD4) and the second binding domain is SCFv(12b), does not reasonably provide enablement for neutralizing bispecific fusion proteins capable of binding to an inducing site on gp120 (CD4 binding site) thereby exposing an induced epitope of gp120 (co-receptor binding site) and a second binding domain capable of forming a neutralizing complex with the induced epitope wherein the first binding domain is anything other than sCD4 (soluble CD4) and/or the second binding domain is anything other than SCFv(12b). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims without undue experimentation.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

The factors include, but are not limited to:

1. The breadth of the claims,
2. The nature of the invention,

3. The state of the prior art,
4. The level of one of ordinary skill,
5. The level of predictability in the art,
6. The amount of direction provided by the inventor,
7. The existence of working examples, and
8. The quantity of experimentation needed to make and/or use the invention based on the content of the disclosure.

The instant claims are drawn to neutralizing bispecific fusion proteins capable of binding to an inducing site on gp120 (CD4 binding site) thereby exposing an induced epitope of gp120 (co-receptor binding site) and a second binding domain capable of forming a neutralizing complex with the induced epitope wherein the first binding domain is derived from a CD4 molecule and the second binding domain comprises a variable region of an antibody heavy or light chain. In order to practice the claimed invention one must know not only what CD4 "derivatives" would be capable of exposing an "induced epitope" one must also know what "antibody variable region" would be able to bind to said epitope resulting in the "neutralization" of the gp120 activity (i.e. HIV-1 infectivity). The specification prophetically states, "the first binding domain can be a ligand such as CD4 or fragments thereof" (see page 4, lines 6-7) and "molecules derived from CD4 include fragments of CD4, generated by either chemical (e.g. enzymatic) digestion or genetic engineering means. Such a fragment may be one or more entire CD4 proteins (for example, extracellular domains D1, D2, D3 and D4) as defined in the immunological literature or a portion of one or more of these well defined domains" (see page 8, lines 30-33). However, the specification is silent on what CD4 domains or fragments thereof would expose an induced epitope upon binding to gp120. The specification is equally silent on what "induced epitopes", if any, would be exposed by the binding of a given CD4 derivative (fragment) to gp120. Moreover, the specification is silent on what "variable region of an antibody heavy or light chain" would bind to a given exposed "induced epitope" resulting in the neutralization of gp120 activity. The working

examples provided in the specification disclose methods of making of a single neutralizing bispecific fusion protein, sCD4-SCFv(17b) [see Examples 1-2 and 4]. Said working examples also demonstrate that sCD4-SCFv(17b) strongly inhibited HIV-1 Env-mediated cell fusion through the neutralization of gp120 activity.

Protein chemistry and immunology are probably the most unpredictable areas of biotechnology Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). This is especially true for antibodies where a single amino acid change can alter the specificity of an antibody. Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, column 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is

context dependent, and both molecular and cellular aspects have to be considered (p. 398, column 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, column 3). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, column 2). Most features predicted with an accuracy of greater than 70% are of structural nature and, at best, only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399, paragraph bridging columns 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those features are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, paragraph bridging cols 1 and 2). Clearly, given not only the teachings of Bowie et al. but also the limitations and pitfalls of using computational sequence analysis and the unknown effects the cellular context on protein function as taught by Bork, the claimed proteins could not be predicted based on unknown sequences. Further, even if a given polypeptide (fusion protein) possesses all the structural limitations of the claimed invention, neither the specification nor any art of record teaches whether said polypeptide would function in the manner recited in the claims. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to make/use neutralizing bispecific fusion proteins capable of binding to an inducing site on gp120 (CD4 binding site) thereby exposing an induced epitope of gp120 (co-receptor binding site) and a second binding domain capable of forming a neutralizing complex with the induced epitope wherein the first binding domain is derived from a CD4 molecule and the second binding domain comprises a variable region of an antibody heavy or light chain. While the level of skill in the arts of protein chemistry and immunology is high, one of skill in the art would not be able to predict which "portions" of CD4 would

be required to expose an "induced epitope" nor would one of skill in the art be able to predict which antibodies or fragments thereof (i.e. binding domains comprising heavy or light chains of antibodies) would be capable of not only binding the exposed epitope but neutralizing the ability of gp120 to function properly (resulting in the neutralization of HIV-1 infectivity). In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

Claims 49 and 55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The aforementioned claims are drawn to pharmaceutical compositions (claim 49) and kits containing pharmaceutical compositions (claim 55). The specification however, is silent on how such a composition would be used and equally silent on the efficacy of said compositions. People of skill in the art require evidence that a benefit can be derived by the application of a given substance. The specification, as filed, does not set forth that the claimed compositions provide any sort of therapeutic effect in any model system that can be applied (or extrapolated) to humans or higher mammals (or in humans themselves). The specification describes (prophetically, in most instances) how a given fusion protein composition can be made but is silent on its therapeutic use. While the skill in the art of immunology is high, to date, prediction of a therapeutic benefit (effect) for any given composition is quite unpredictable. Moreover, while one may know how to make the composition (as is the case with sCD4-SCFv(12b)), no evidence has been provided that illustrates or even suggest that the claimed pharmaceutical

compositions are capable of eliciting a beneficial response, one of skill in the art has not been taught to use the claimed composition as a pharmaceutical, as is required by the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 33-34 and 37 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 33 recites the limitation "functional recombinant" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 37 is vague and indefinite as it is dependent on a non-elected claim. Consequently, it is impossible to determine the metes and bounds of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 11-12, 14-19, 23-34, 37, 48-49 and 52-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Traunecker et al. (International Journal of Cancer, Supplement 7, 1992, pages 51-52 – IDS-6) in view of Sullivan et al. (Journal of Virology, Vol. 72, No. 6, 1998, pages 4694-4703 – IDS-6).

The instant claims are drawn to for neutralizing bispecific fusion proteins capable of binding to an inducing site on gp120 (CD4 binding site) thereby exposing an induced epitope of gp120 (co-receptor binding site) and a second binding domain capable of forming a neutralizing complex with the induced epitope wherein the first binding domain is derived from a CD4 molecule and the second binding domain comprises a variable region of an antibody heavy or light chain and the first and second binding domains are separated by a linker (optionally, at least one occurrence of SEQ ID NO:1 or SEQ ID NO:2). Moreover, the second binding domain can be

derived from the antibodies 12b, CG10 and 48d and may be in the form of a single-chain Fv (SCFv).

Traunecker et al. disclose single chain bispecific reagents (fusion proteins) wherein the first binding domain is derived from soluble CD4 (sCD4) and the second binding domain is derived from the Fv domain of an anti-CD3 antibody. Traunecker et al. further the two binding domains are joined by a polypeptide linker. Traunecker et al. differs from the instant invention in that they do not explicitly disclose the use antibody binding domains that bind to an induced epitope of gp120 (i.e. 12b, CG10 and 48d) as the second binding domain nor do they disclose the use of linkers with the sequence of either SEQ ID NO:1 or SEQ ID NO:2. Sullivan et al. disclose the use of sCD4 in conjunction with neutralizing antibodies (12b and CG10) to inhibit (neutralize) the activity of gp120 (see abstract). Sullivan et al. further disclose that the 12b and CG10 binding epitopes are exposed by the binding of sCD4 to gp120 (see abstract, page 4695 and pages 4696-4697). Moreover, Sullivan et al. disclose that sCD4 dramatically enhanced the neutralizing ability of the 12b and CG10 antibodies (see pages 4700-4701). Finally, Sullivan et al. disclose that the gp120 binding epitopes for 12b and CG10 are well conserved and are present on a multitude of wild-type HIV-1 isolates (see pages 4695 and 4697-4699). Consequently, it would have been obvious to substitute the anti-CD3 binding domains in the sCD4-FvCD3 bispecific fusion protein disclosed by Traunecker et al. with the binding domains of either the 12b or CG10 antibody disclosed by Sullivan et al. in order to take advantage of the ability of the resulting antibodies to neutralize the infectivity (gp120 activity) of a wide variety of wild-type HIV-1 isolates and the reduced number of escape mutants that would result in any *in vivo* application of the bispecific fusion protein disclosed by Traunecker et al. Moreover, the

bispecific fusion proteins of Traunecker et al. "provide efficient transport of these molecules as cell-bound entities to the sites of infection and thus the functional half-lives of these molecules can be made greater than those of free soluble molecules (see page 52). Finally, an sCD4-12b or sCD4CG10 fusion protein would eliminate the increase in virus entry or syncytium formation sometimes associated with sCD4 alone (see Sullivan et al. page 4695). One of skill in the art would have had high expectation of success since Traunecker et al. disclose that their "approach to design single-chain molecules can be applied more generally". It should be noted that linkers disclosed by Traunecker et al. do not have the sequence of either SEQ ID NO:1 or SEQ ID NO:2. However, the use of linkers is well known in the art and, in the absence of evidence to the contrary, the use of linkers with the sequence of either SEQ ID NO:1 or SEQ ID NO:2 would be obvious to one of ordinary skill in the art when maintaining the spatial orientation of CD4 and either the 12b or CG10 binding domains with their respective gp120 binding epitopes. It would be equally obvious to one of ordinary skill in the art to package the aforementioned claimed fusion protein in a kit bundled with instructions in order to facilitate ease of use and reduce cost.

Claims 1, 11-12, 14-19, 23-34, 37, 48-49 and 52-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Traunecker et al. (International Journal of Cancer, Supplement 7, 1992, pages 51-52 – IDS-6) in view of Thali et al. (Journal of Virology, Vol. 67, No. 7, 1993, pages 3978-3988 – IDS-6).

The instant claims are drawn to for neutralizing bispecific fusion proteins capable of binding to an inducing site on gp120 (CD4 binding site) thereby exposing an induced epitope of gp120 (co-receptor binding site) and a second binding domain capable of forming a neutralizing

complex with the induced epitope wherein the first binding domain is derived from a CD4 molecule and the second binding domain comprises a variable region of an antibody heavy or light chain and the first and second binding domains are separated by a linker (optionally, at least one occurrence of SEQ ID NO:1 or SEQ ID NO:2). Moreover, the second binding domain can be derived from the antibodies 12b, CG10 and 48d and may be in the form of a single-chain Fv (SCFv).

Traunecker et al. disclose single chain bispecific reagents (fusion proteins) wherein the first binding domain is derived from soluble CD4 (sCD4) and the second binding domain is derived from the Fv domain of an anti-CD3 antibody. Traunecker et al. further the two binding domains are joined by a polypeptide linker. Traunecker et al. differs from the instant invention in that they do not explicitly disclose the use antibody binding domains that bind to an induced epitope of gp120 (i.e. 12b, CG10 and 48d) nor do they disclose the use of linkers with the sequence of either SEQ ID NO:1 or SEQ ID NO:2. Thali et al. disclose the use of sCD4 in conjunction with neutralizing antibodies (12b and 48d) to inhibit (neutralize) the activity of gp120 (see abstract). Thali et al. further disclose that the 12b and 48d binding epitopes are exposed by the binding of sCD4 to gp120 (see abstract and page 3983-3984). Moreover, Thali et al. disclose that the gp120 binding epitopes for 12b and 48d are well conserved and are present on a multitude of wild-type HIV-1 isolates (see page 3984). Consequently, it would have been obvious to substitute the anti-CD3 binding domains in the sCD4-FvCD3 bispecific fusion protein disclosed by Traunecker et al. with the binding domains of either the 12b or 48d antibody disclosed by Thali et al. in order to take advantage of the ability of said antibodies to neutralize the infectivity (gp120 activity) of a wide variety of wild-type HIV-1 isolates and the reduced

number of escape mutants that would result in any *in vivo* application of the bispecific fusion protein disclosed by Traunecker et al. Moreover, the bispecific fusion proteins of Traunecker et al. "provide efficient transport of these molecules as cell-bound entities to the sites of infection and thus the functional half-lives of these molecules can be made greater than those of free soluble molecules (see page 52). One of skill in the art would have had high expectation of success since Traunecker et al. disclose that their "approach to design single-chain molecules can be applied more generally". It should be noted that linkers disclosed by Traunecker et al. do not have the sequence of either SEQ ID NO:1 or SEQ ID NO:2. However, the use of linkers is well known in the art and, in the absence of evidence to the contrary, the use linkers with the sequence of either SEQ ID NO:1 or SEQ ID NO:2 would be obvious to one of ordinary skill in the art when maintaining the special orientation of CD4 and either the 12b or 48d binding domains with their respective gp120 binding epitopes. It would be equally obvious to one of ordinary skill in the art to package the aforementioned claimed fusion protein in a kit bundled with instructions in order to facilitate ease of use and reduce cost.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (703) 308-7991. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Robert A. Zeman
November 20, 2003